Claims 1-15 were rejected as obvious over the Plowman et al reference in the January 17, 1987 publication of The Lancet (Lancet). The Examiner has incorrectly applied the limited teachings of the Lancet reference, and it is respectfully submitted that no *prima facie* case of obviousness has been presented. To establish a case of *prima facie* obviousness, the Examiner must fulfill three criteria: 1) There must be some suggestion or motivation in the reference or known to those skilled in the art to modify the reference; 2) a reasonable expectation of success; and 3) the prior art must teach each and every claim limitation.

First, contrary to the conclusions of the Examiner, with regard to Claims 1-4 the Lancet reference does not teach or suggest administration of mesna or other sulfhydryl compounds as therapy for radiation exposure. The bare disclosure found in the Lancet reference is that mesna afforded, at first glance, about 10% radioprotection. No teaching is found in the article that suggests mesna (the only compound mentioned) may be useful as therapy for radiation exposure. The Lancet reference does teach "We are now looking at administration and the timing and dose of mesna in respect of radioprotection achieved." This suggests that Plowman, et al. had no idea as yet what constituted an "effective amount" for purposes of therapy, as claimed in Claim 1 of this application.

Second, with regard to the formula I compounds, again only mesna is mentioned. Passing mention of "similar sulphydryl-containing molecules" teaches nothing to one skilled in the art.

Third, the Lancet reference does not teach the concept of therapy for radiation protection. The only suggestion in the Lancet article with any relevance to this application is that mesna is a radioprotector. This was not a new statement at the time of publication of the Lancet reference in 1987, as sulfhydryl compounds were believed to afford radioprotection

since their discovery more than a decade earlier. However, merely publishing a possible use of a particular composition does not equate to the level of motivating others skilled in the art to modify or adopt those teachings, particularly when the purpose of the publication is not to suggest that use, but rather to warn other clinicians of the dangers of the presence of mesna in the patient at the time of total body irradiation. This warning suggests the opposite of what the Claims of the subject application teach- administering an effective amount of a formula I compound as therapy for radiation exposure. The Lancet reference instead teaches one skilled in the art to avoid the presence of mesna during radiation therapy, by waiting at least 12 hours after mesna infusion to do TBI.

With regard to Claims 5-13, again the Lancet reference teaches directly away from the Claimed method. Waiting 12 hours after mesna infusion prior to commencing radiotherapy teaches exactly the opposite of these Claims, which recite a prophylactic treatment for a patient by ensuring that mesna is present in the patient's body at the time of radiotherapy. Claims 7, 10 and 11 of the subject application further describe the dosing regimen to ensure the constant presence of mesna in the patient's body to, which is doubly contrary to the Lancet reference teachings. suggest insertion of dosing into ind. claims.

With regard to Claims 14 and 15, the rejection of these claims is unjustified and not supported by evidence or by inference. The Examiner makes no specific reference to these claims at all, which is telling in that both Claims 14 and 15 define only formula I compounds that are not thiols (sulfhydryls, where R_1 is hydrogen) within their given structures. Thioethers (R_1 is lower alkyl), disulfides (R_1 is -S-alkyl-R_4 and others), and conjugates (R_1 is a sulfur-containing amino acid) are not even mentioned in the Lancet reference, nor in the current Office Action. There is no basis or justification for the rejection of Claims 14 and 15.

Regarding the reasonable expectation of success requirement, the Lancet reference also fails. The only mention in the publication as to administration of mesna in combination with radiotherapy is that such a combination is undesirable, as argued above. Even were this teaching not included in the Lancet reference, one skilled the art would hardly be motivated to use mesna because of the published "10% radioprotection." Applicant searched for subsequent publications by the Lancet and other sources concerning these authors and this subject but none were found.

Finally, the Lancet reference fails to establish any case of obviousness because it fails to teach or suggest all of the claim limitations. Specifically lacking is any teaching as to what constitutes an "effective amount" for either therapeutic or prophylactic purposes. The Lancet reference teaches only that mice receive "significantly improved survival" upon being given "the median lethal dose (LD_{50})" of total body irradiation. Anyone skilled in the pharmaceutical arts knows that LD_{50} tests are essentially useless when attempting to formulate an effective amount for either therapy or prophylaxis.

Applicant also submits that the Examiner has confused the issues in this case by referring to two disparate art fields in discerning the skill level of the art. Applicant submits that the proper art field to determine the level of skill here is the pharmaceutical arts, not the radiology arts or formulation chemistry arts.

In conclusion, no *prima facie* case of obviousness has been established based on The Lancet reference for the following reasons- 1) There is no suggestion to amplify The Lancet's limited teaching of a of a known fact (mesna is a radioprotector) to the claimed method for treating/protecting a patient against radiation exposure; 2) there is no reasonable expectation that the method disclosed in the reference would be successful in doing anything other

improving survival by 10% in those given a lethal dose of radiation; and 3) even if the reference could somehow be read to teach a method of treating/protecting against radiation exposure, the reference fails because it does not teach or suggest all of the claim limitations, e.g., nowhere in reference is there any teaching or suggestion of what an effective amount of a formula I compound would entail.

Favorable reconsideration for all claims is respectfully solicited. Should the Examiner desire the need to communicate with the undersigned attorney, a newly issued direct dial number is noted below.

Respectfully submitted,

Thomas J. Dodd
Senior Patent Counsel
BioNumerik Pharmaceuticals, Inc.
Attorney for Applicant(s)
Registration No. 31,010
Phone: 210-581-8082

BioNumerik Pharmaceuticals, Inc.
8122 Datapoint Drive, Suite 1250
San Antonio, Texas 78229
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